Contains Nonbinding Recommendations

Draft Guidance on Phenytoin Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Phenytoin sodium

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Four studies

1. Type of study: Fasting
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 100mg (dose: 3 X 100mg)
   Subjects: Normal healthy males and females, general population
   Additional comments: Washout period of at least 14 days. The strength(s) designated in the Orange Book as the reference listed drug (RLD) should be used in the studies. The applicant should use the reference-scaled average bioequivalence (BE) approach for phenytoin sodium

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 100mg (dose: 3 X 100mg)
   Subjects: Normal healthy males and females, general population
   Additional comments: See comments above

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3. Type of study: Fasting
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 30mg (dose: 10 X 30mg)
   Subjects: Normal healthy males and females, general population
   Additional comments: See comments above

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4. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 30mg (dose: 10 X 30mg)
   Subjects: Normal healthy males and females, general population
   Additional comments: See comments above

Analytes to measure: Phenytoin in plasma

Bioequivalence based on (90% CI): Phenytoin

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times:

Conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

In addition to the method above, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Explanation: FDA has concluded that phenytoin is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between the effective phenytoin concentrations and the concentrations associated with serious toxicity is narrow
- Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity
- Phenytoin is subject to therapeutic monitoring based on pharmacokinetics measures
- Phenytoin has low-to-moderate within-subject variability
- Doses are adjusted in small increments (less than 20%) in clinical practice

The study should be a fully replicated crossover design in order to:

- Scale BE limits to the variability of the reference product
- Compare test and reference product within-subject variability

For details about the Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for NTI drugs, refer to *Draft Guidance on Warfarin Sodium*.